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05 DEC 1998 P01/7700 0.00 - 9826700.8

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1. Your reference — P1339

2. Patent application number *(The Patent Office will fill in this part)* — **9826700.8**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

UNIVERSITY OF DURHAM
SOUTH ROAD
DURHAM DH1 3LE

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — 7085256001

4. Title of the invention — PROCESS FOR PREPARING CHIRAL COMPOUNDS

5. Name of your agent *(if you have one)* — MARKGRAAF PATENTS LIMITED

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

The Crescent
54 Blossom Street
YORK
YO24 1AP

Patents ADP number *(if you know it)* — 7296486002

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

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a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

YES

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Continuation sheets of this form	
Description	22
Claim(s)	
Abstract	
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Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Markgraaf Patents Ltd Date 04.12.1998

MARKGRAAF PATENTS LIMITED

12. Name and daytime telephone number of person to contact in the United Kingdom — Philippa M Allen — 01904 610586

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PROCESS FOR PREPARING CHIRAL COMPOUNDS

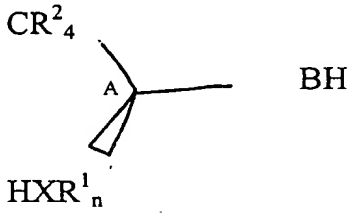
The present invention relates to a process for the preparation of a class of enantiomerically pure chiral compounds, the compounds obtained thereby and novel compounds, compositions thereof and the use thereof as or in the preparation of a pharmaceutical, veterinary product, agrochemical, polymer, library of compounds and their respective intermediates.

Efficient and simple synthesis of known and novel compounds can be the key to commercial success and may also lead to further development and discoveries enabled by availability of compounds in significant purities, yields and the like. Nevertheless development of new synthetic routes is costly and time consuming, without the guarantee of success.

We have now surprisingly found a process for synthesising a class of compounds in novel manner to produce enantiomerically pure hetero compounds.

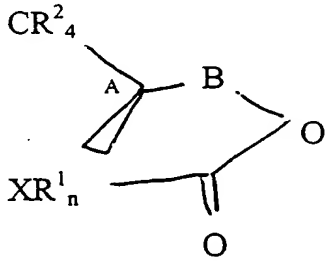
Accordingly in a first aspect there is provided a process for the preparation of chiral compounds of formula I:

(I)



comprising contacting a compound of formula II:

(II)



with a source of hydrogen or fluorine;

wherein A is a chiral centre;

X is selected from oxygen, sulphur and nitrogen;

n is selected from 0 and 1 and is equal to the valence of X less 2;

Each R^1 is independently selected from hydrogen, straight chain and branched, saturated and unsaturated C_{1-8} hydrocarbon optionally substituted by one or more hydroxy, halo, aryl, cyclo C_{1-8} alkyl and the like;

B is a fragment CR^3_2 wherein each R^3 is independently selected from O-, N- and S- containing functional groups such as hydrogen, halo, azides and cyanides; straight and branched chain, saturated and unsaturated C_{1-4} alkyl, alkenyl and alkynyl and aryl, each optionally substituted by hydroxy, halo, saturated or unsaturated C_{1-4} alkyl, alkenyl or alkynyl, aryl, cyclo C_{1-6} alkyl, carbonyl, carboxyl, amino, amido, (thio)ether, haloalkyl, silylalkyl and the like;

each R^2 is independently selected from hydrogen, straight chain and branched, saturated and unsaturated C_{1-8} alkyl, optionally substituted by hydroxy, halo, aryl, cyclo C_{1-6} alkyl, carbonyl, carboxyl, amino, amido, (thio)ether and the like; and

one of R^1 and one of R^2 together may form an alkylene group as part of a heterocyclic ring;

with the proviso that when X is nitrogen, n is 2, one of R^1 and two of R^2 are hydrogen, B is $CHPh_2$, the other R^1 and R^2 do not form together a five membered heterocyclic ring.

Preferably X is nitrogen whereby n is 1.

Preferably B is a fragment CR^3_2 wherein R^3 is selected from ethenyl, propenyl ethynyl and propynyl, optionally substituted phenyl, for example 4-methoxy or 4-perfluoryl alkyl phenyl, naphthyl, methyl phenyl and the like.

More preferably B is a group as hereinbefore defined wherein at least one and preferably both of R^3 are aryl, more preferably optionally substituted phenyl.

Preferably R^2 is selected from optionally hydroxy, halo, alkoxy substituted branched and straight chain C_{1-6} alkyl, including methyl i-propyl, i-butyl, t-butyl; and aryl including phenyl and benzyl.

Preferably X is nitrogen wherein n is one and R^1 does not form a cyclic ring with one of R^2, i.e. the compound is a non cyclic secondary amine, or R^1 is H, and R^2 is other than H, i.e. the compound is a primary amine.

Contacting the compound of formula II as hereinbefore defined is suitably in the presence of a catalyst which may be homogeneous or heterogeneous, and is preferably heterogeneous.

Without being limited to this theory it is thought that the conversion according to the process of the invention proceeds via a substitution with subsequent decarboxylation or decarboxylation with subsequent quenching. The catalyst may be selected from any catalyst suitable for the conversion as hereinbefore defined. Preferably the catalyst comprises a hydrogenation or fluorination catalyst or agent. A hydrogenation catalyst suitably comprises a metal adapted to catalyse a hydrogenation reaction, for example selected from the transition metals of Group VIII of the Periodic Table of the Elements, preferably selected from Pt, Pd, Ni, Co, Cu, Ru, Fe and Ag and mixtures thereof. The catalyst may be in the form of the metal(s) or salts thereof, optionally in the presence of or

including additional catalytic components or catalytic supports such as C. More preferably the catalyst comprises palladium and carbon, and reaction is in the presence of gaseous hydrogen.

The catalyst is present in catalytically effective amount.

The process may be carried out with use of solvents, and may be carried out at ambient or elevated temperature and/or pressure, and is preferably carried out at elevated pressure in the range 1-10 atm.

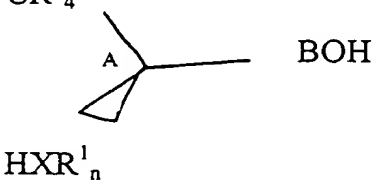
The process of the invention is preferably suited for the preparation of pharmaceutical, veterinary product, agrochemical and polymeric compounds and libraries of such compounds, and their synthetic intermediates. It is a particular advantage of the process of the invention that such compounds may be readily prepared in which B is analogous electronically and/or sterically to characteristic groupings in known pharmaceutical, veterinary product and agrochemicals. The process therefore provides a known route to access compounds and whole ranges of new analogues, wherein the group B is as hereinbefore defined.

Alternatively the process as hereinbefore defined is suited for the preparation of metal complexes as asymmetric catalysts.

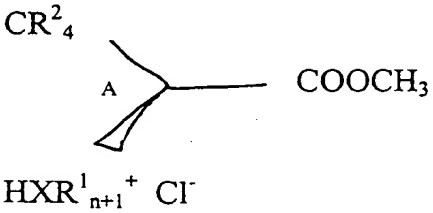
In a further aspect of the invention there is provided a class of novel enantiomerically pure chiral hetero compounds of the formula I as hereinbefore defined wherein A, B and R^1 are as hereinbefore defined, X is N and n is 1 with the exception that R^2 is not phenyl or benzyl when R^1 is hydrogen and BH is phenyl or CH_3.

Compounds of the formula II as hereinbefore defined may be obtained commercially or prepared by known means. Akiba *et al*, Tetrahedron, 1994, 50

(13), 3905 discloses the preparation of a compound of formula II by cyclisation of amino alcohol with trichloromethyl chloroformate ($Cl_3COCOCl$) in the presence of triethylamine (Et_3N). Using this process compounds of formula II are obtained from compounds of formula III:

(III) 

Intermediate compounds of formula III as hereinbefore defined may be obtained commercially or using the process, for example of Gawley and Zhang, J. Org. Chem., 1996, 61, 8103, and Itsuno *et al*, J. Chem. Soc., Perkin Trans. I, 1985, 2039. In these publications is taught the preparation of a compound of formula III as hereinbefore defined by reaction of a compound of formula IV:

(IV) 

with a compound of formula V:

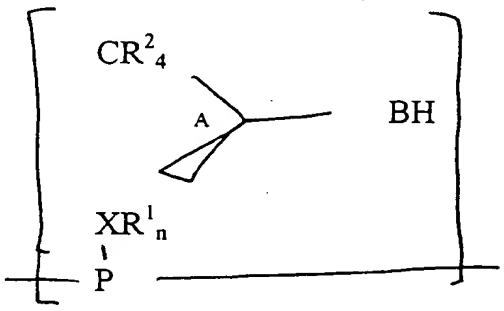
(V) R^2MgBr.

Reaction is preferably under reflux in cold solvent.

Compounds of formula IV and V are commercially available or may be synthesised by known means.

In a further aspect of the invention there is provided a process for the preparation of enantiomerically pure chiral polymers comprising a repeating unit of the formula Ii:

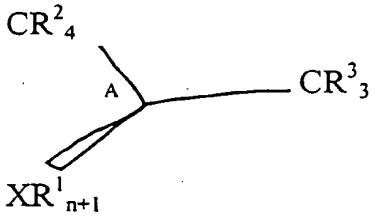
(Ii)



wherein P is derived from a polymerisable monomer or oligomer and X, R^1, R^2, B and A are as hereinbefore defined.

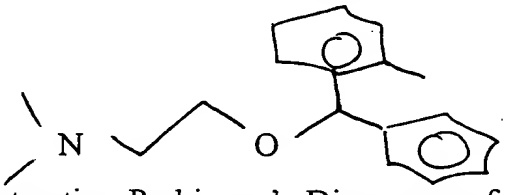
Polymerisable monomers may be any known monomers, for example selected from monomers of thermoset and thermoplast polymers and mixtures thereof, including monomers preferably selected from the group consisting of: an epoxy resin such as an epoxy resin derived from the mono or poly-glycidyl derivative of one or more of the group of compounds consisting of aromatic diamines, aromatic monoprimary amines, aminophenols, polyhydric phenols, polyhydric alcohols, polycarboxylic acids and the like; an addition-polymerisation resin, such as a bis-maleimide resin, acrylic, vinyl or unsaturated polyester; a formaldehyde condensate resin, such as a formaldehyde-phenol resin, urea, melamine or phenol resin; a cyanate resin; and an isocyanate resin; polyaromatics such as polysulphones and polyethersulphones; monomers of natural polymers including carbohydrates, polypeptides and proteins including starch, celluloses, collagen, gelatin, dextrans, alginates, chitin and chitosan; and monomers of biodegradeable and/or biocompatible polymers such as polyesters including poly(lactic acid), poly(glycolic acid), polycaprolactone and the like, polyorthoesters, polyanhydrides, polyaminoacids and azo polymers, for example for the delivery of a pharmaceutical, veterinary product or agrochemical *in situ* .

In a further aspect of the invention there is provided a process for the preparation of compounds of the formula Iii:

(Iii) 

by the functional modification of a compound of formula I as hereinbefore defined to include additional groups R^1 and R^3 or the interconversion of one compound of formula I as hereinbefore defined to another compound of formula I as hereinbefore defined.

Preferably the compound of formula Iii as hereinbefore defined is a spatial, electronic or reactive analogue of a known pharmaceutical, veterinary product, or agrochemical, for example of a neuro active compound, such as the compound orphenadrine of formula:



for use in treating Parkinson's Disease or of cardiovascular or gastro-intestinal drugs, immunosuppresants, respiratory agents, muskuloskeletal and joint disease drugs, immunological products and vaccines, pest control agents, plant growth control agents, plant disease control agents and the like.

In a further aspect of the invention there is provided the use of one or more compounds of formula I as hereinbefore defined in the preparation of a library of compounds comprising:

reacting one or more compounds of formula I as hereinbefore defined with one or more substrates which are supported or contained in solid or liquid phase each on an individual support or within an individual vessel; and

labelling the support or vessel with means to identify the synthetic history of the supported or contained compound.

The process for preparing a library of compounds may employ any techniques as known in the art of combinatorial chemistry.

In a further aspect of the invention there is provided a process for the preparation of a library of compounds of formula I as hereinbefore defined comprising:

reacting one or more compounds of formula IV as hereinbefore defined with a plurality of compounds of formula V as hereinbefore defined, and converting via compounds of formula II as hereinbefore defined to compounds of formula I as hereinbefore defined; and

optionally labelling the support or vessel with means to identify the synthetic history of the supported or contained compound.

In a further aspect of the invention there is provided a library of compounds of formula I, II or III as hereinbefore defined.

Preferably the library of compounds is suitable for any of the hereinbefore defined uses. The library may be provided in the form of a kit of sample boxes for the intended use. The library may contain two or more compounds, for example ten or more compounds, preferably comprises 50-1,000 compounds of

any given formula as hereinbefore defined, optionally including synthetic history identification.

In a further aspect of the invention there is provided a pharmaceutical, veterinary product or agrochemical composition comprising a compound of formula I as hereinbefore defined or derivatives thereof together with suitable diluents, adjuvants, carriers and the like.

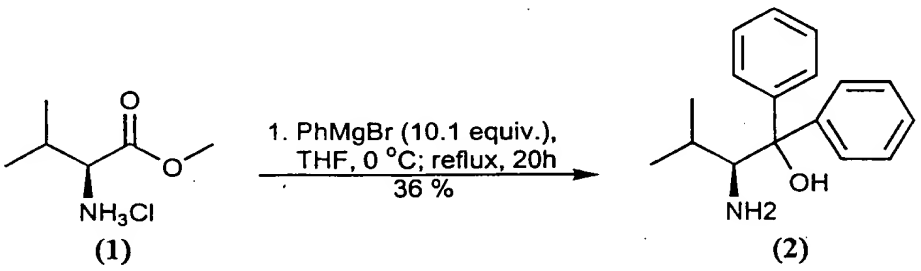
The invention is now illustrated in non limiting manner with reference to the examples.

Examples

1.1 New Synthetic Approach to Novel Chiral Amines

1.1.1 Synthesis of (S)-2-amino-1,1-diphenyl-3-methyl-1-butanol (2)

The title compound **(2)** was readily prepared by the addition of L-valine methyl ester hydrochloride **(1)** to phenylmagnesium bromide, as depicted in **Scheme 1**, following the modified method described by Gawley[i] and Zhang (1996), and Itsuno[ii] *et al.* (1985).



(1) **(2)**

Scheme 1

Purification over silica gel, gave **(2)** as a white solid in moderate yield (36 %).

1.1.2 Synthesis of (S)-4-isopropyl-5,5-diphenyl-2-oxazolidinone (3)

In the event, the title compound **(3)** was readily prepared by the cyclisation of aminoalcohol **(2)** with trichloromethyl chloroformate ($Cl_3COCOCl$) in

the presence of triethylamine (Et_3N), as shown in **Scheme 2**, following the method described by Akiba[iii] *et al.* (1994).

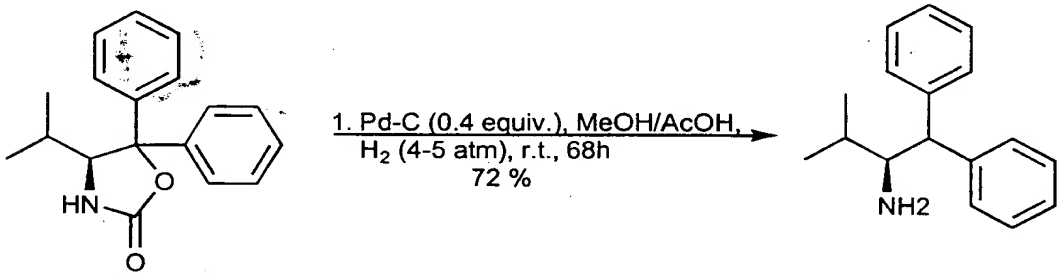
(2) **(3)**

Scheme 2

Upon work-up, the solid residue was loaded on to a sintered funnel and then washed with diethyl ether to obtain the title compound **(3)** as a white solid in good yield (86 %).

1.1.3 Synthesis of (S)-2-amino-3-methyl-1,1-diphenylbutane (4)

In the presence of a catalytic amount of palladium on activated carbon, 2-oxazolidinone **(3)** was finally submitted to the hydrogenation in a mixture of AcOH and MeOH under 4-5 atm. pressure, as illustrated in **Scheme 3**.



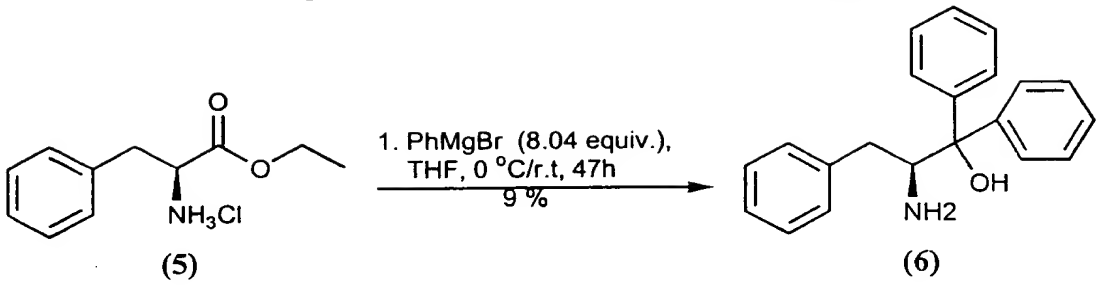
(3) **(4)**

Scheme 3

Upon filtration and re-crystallisation from petroleum ether, the title compound **(4)** was generated as a white solid in good yield (72 %).

1.1.4 Synthesis of (S)-2-amino-1,1,3-triphenyl-1-propanol (6)

The title compound **(6)**, following the modified literature methods of Itsuno[ii,iv] *et al.* (1985), Weber[v] *et al.* (1995) and Dammast and Reißig[vi] (1993), was readily prepared by the portionwise addition of L-phenylalanine ethyl ester hydrochloride **(5)** to phenylmagnesium bromide, as depicted in **Scheme 4**.



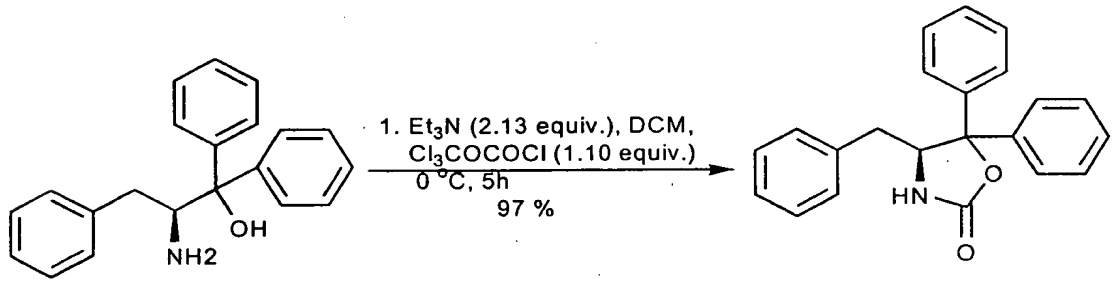
(5) (6)

Scheme 4

Recrystallisation gave the title compound **(6)** as a white solid in low yield (9 %). [Phillipa, this yield is not representative, but represents what happened on the day, it could clearly be improved and should not be reported]

1.1.5 Synthesis of (S)-4-benzyl-5,5-diphenyl -2-oxazolidinone (7)

In the event, the title compound (7) was readily prepared by the cyclisation of aminoalcohol **(6)** with trichloromethyl chloroformate ($Cl_3COCOCl$) in the presence of triethylamine (Et_3N), as shown in **Scheme 5**, following the method described by Akiba[iii] *et al.* (1994).



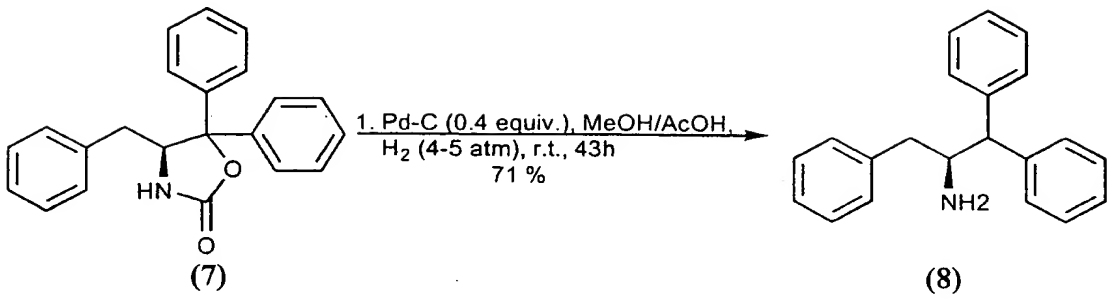
(6) (7)

Scheme 5

Upon work-up, the solid residue was loaded on to a sintered funnel and then washed with diethyl ether to obtain the title compound **(7)** as a white solid in excellent yield (97 %).

1.1.6 Synthesis of (S)-2-amino-1,1,3-triphenyl-propane (8)

In the presence of a catalytic amount of palladium on activated carbon, 2-oxazolidinone **(7)** was finally subjected to the hydrogenation in a mixture of AcOH and MeOH under 4-5 atm. pressure, as illustrated in **Scheme 6**.



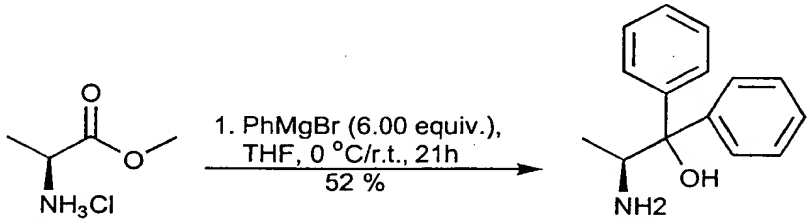
(7) (8)

Scheme 6

Upon filtration and purification over silica gel, eluting with a 3:7 and 4:6 mixture of AcOEt and petrol, the title compound **(8)** was obtained as a light-brown solid in good yield (71 %).

1.1.7 Synthesis of (S)-2-amino-1,1-diphenyl-1-propanol (10)

The title compound **(10)**, following the literature methods of Itsuno[ii] *et al.* (1985), Weber[v] *et al.* (1995) and Dammast[vi] and Reißig (1993), was readily prepared by the portionwise addition of L-alanine methyl ester hydrochloride **(9)** to phenylmagnesium bromide, as depicted in **Scheme 7**.



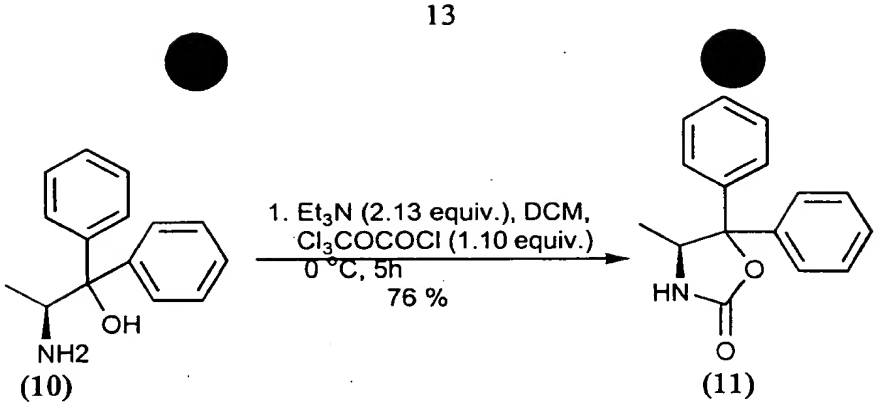
(9) (10)

Scheme 7

Flash column chromatography, eluting with dichloromethane and then further elution with a mixture of AcOEt and petrol, ranging from 15 % up to 100 %, gave the title compound **(10)** as a white solid in moderate yield (52 %).

1.1.8 Synthesis of (S)-4-methyl-5,5-diphenyl-2-oxazolidinone (11)

In the event, the title compound **(11)** was readily prepared by the cyclisation of aminoalcohol **(10)** with trichloromethyl chloroformate ($Cl_3COCOCl$) in the presence of triethylamine (Et_3N), as shown in **Scheme 8**, following the method described by Akiba[iii] *et al.* (1994).



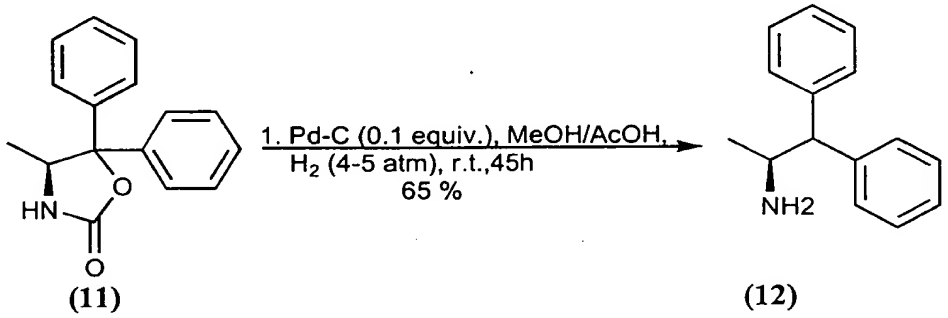
(10) (11)

Scheme 8

Upon work-up, the solid residue was loaded on to a sintered funnel and then washed with diethyl ether to obtain the title compound **(11)** as a white solid in good yield (76 %).

1.1.9 Synthesis of (S)-2-amino-1,1-diphenyl-propane (12)

In the presence of a catalytic amount of palladium on activated carbon, 2-oxazolidinone **(11)** was finally subjected to the hydrogenation in a mixture of AcOH and MeOH under 4-5 atm. pressure, as illustrated in **Scheme 9**.



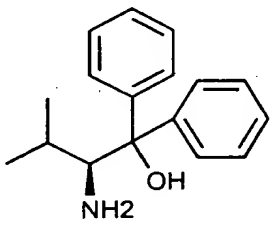
(11) (12)

Scheme 9

Upon filtration and purification by dry-flash column chromatography, eluting first with AcOEt, and then with a mixture of MeOH and AcOEt, ranging from 5 % up to 30 %, gave the title compound **(12)** as a white solid in moderate yield (71 %).

1.2 Experimental

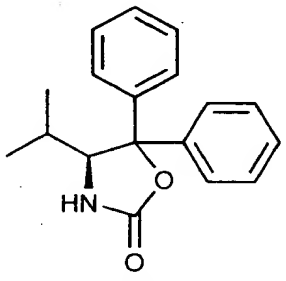
1.2.1 (S)-2-amino-1,1-diphenyl-3-methyl-1-butanol (2)



(2)

L-Valine methyl ester hydrochloride (9.9 g, 59.06 mmol) was added portionwise to a 1.0 M solution of phenylmagnesium bromide (108.8 g, 0.6 mol) in THF at 0 °C and heated at reflux for 20h. After quenching with crushed ice and NH_4Cl salt, the organic layer was separated, washed with brine and concentrated under reduced pressure. The resulting solid was treated with HCl (2.0 M, 100 ml) and then evaporated to dryness under reduced pressure. Impurities precipitated out as a white solid, when the amine hydrochloride salt was dissolved in hot MeOH and allowed to cool to room temperature. After removing the impurities by filtration, the filtrate was made basic with KOH (1.0 M) and the organics were extracted into diethyl ether (4x100 ml). Combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to obtain a crude product as a light brown solid. Purification over silica gel, eluting with a 1:4 and 1:1 mixture of ethyl acetate and petrol gave the title compound **(2)** (5.42 g, 36 %) as a white solid. m.p. 90-92 °C (lit[i] 94-95 °C). $[\alpha]_D^{25}$ = - 107.92° (c, 0.0424 in $CHCl_3$) (lit[ii]: - 127.7° (c, 0.639 in $CHCl_3$). δ_H 0.81 (3H, d, ^3J= 6.90 Hz, CH_3), 0.85 (3H, d, ^3J= 7.20 Hz), 1.67 (1H, ds, ^3J= 1.80 and 6.90 Hz, CH-Me_2), 3.76 (1H, d, ^3J= 2.10 Hz, CH-NH_2), 7.04-7.58 (10H, m, Ar). δ_C 16.3 and 23.2 (CH_3), 28.1 (CH-Me_2), 60.4 (CH-NH_2), 79.9 (C-OH), 125.7, 126.1, 126.5, 126.8, 128.2 and 128.6 (o-, m- and p-Ar), 145.1 and 148.2 (α-Ar). Anal. Calcld. for $C_{17}H_{21}NO$: C 79.96; H 8.29; N 5.48. Found: C 79.80; H 8.15; N 5.39. ir 3338 (OH and NH_2). m/e (CI-CH_4) 256 (MH^+, 14 %), 72 (100 %).

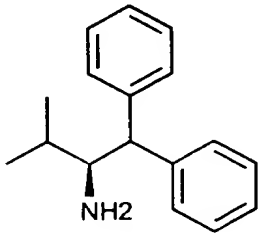
1.2.2 (S)-4-isopropyl-5,5-diphenyl-2-oxazolidinone (3)



(3)

Trichloromethyl chloroformate (2.71 g, 13.7 mmol) was added to a mixture of (S)-2-amino-3-methyl-1,1-diphenyl-1-butanol **(2)** (3.18 g, 12.45 mmol) and triethylamine (2.68 g, 26.52 mmol) in CH_2Cl_2 at 0 °C. The reaction mixture was stirred for 2h at the same temperature and then poured into a brine solution (250 ml). The aqueous layer was made basic with NaOH pellets and organic products were extracted into AcOEt (5x200 ml). Combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude product was washed with diethyl ether to obtain the title compound **(3)** (3.03 g, 86 %) as a white solid. m.p. 250-251 °C (lit. 250-251 °C). $[\alpha]_D^{25}$ = - 201.59° (c, 0.0252 in DMSO). δ_H (DMSO-d_6) 0.51 (3H, d, ^3J= 6.60 Hz, CH_3), 0.92 (3H, d, ^3J= 7.20 Hz, CH_3), 1.86 (1H, ds, ^3J= 2.10 and 6.60 Hz, CH-Me_2), 4.46 (1H, d, ^3J= 6.5 Hz, CH-NH_2), 7.24-7.72 (10H, m, Ar-H), 8.14 (1H, s, NH). δ_C 15.2 and 20.9 (CH_3), 29.8 (CH), 64.9 (CH-NHCO), 88.4 (C-O), 125.8, 126.2, 127.9, 128.4, 128.8 and 129.1 (Ar), 140.5 and 146.1 (α-Ar), 158.1 (C=O). Ir 3295 (NH_2), 1765 and 1745 (C=O). m/e (CI-NH_3) 282 (MH^+, 25 %), 299 (MNH_4^+, 8 %), 238 (96 %), 223 (100 %), 72 (100 %).

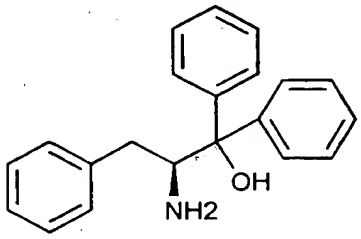
1.2.3 (S)-2-amino-3-methyl-1,1-diphenylbutane (4)



(4)

A solution of (S)-4-isopropyl-5,5-diphenyl-2-oxazolidinone **(3)** (2.9 g, 10.31 mmol) in MeOH/AcOH and a 10 % Pd (435 mg, 4.09 mmol) on activated carbon was shaken for 68h under 4-5 atm pressure of hydrogen at room temperature. The catalyst was filtered off over Hyflo Super Cell and organic solvents were evaporated under reduced pressure. The resulting residue was treated with HCl (2.0 M, 50 ml), stirred for 2h at room temperature, made basic with NaOH pellets, and saturated with K_2CO_3 and NaCl. Organic compounds were then extracted into AcOEt (3x 100 ml), dried over $MgSO_4/K_2CO_3$ and concentrated under reduced pressure to obtain a crude product. Re-crystallisation from petroleum ether gave the title compound **(4)** (1.79 g, 72 %) as a light-brown solid. m.p. 71-72 °C. $[\alpha]_D^{25} = -4.19°$ (c, 0.1097 in $CHCl_3$). δ_H 0.78 (3H, d, ^3J= 6.60 Hz, CH_3), 0.91 (3H, d, ^3J= 7.20 Hz, CH_3), 1.26 (2H, broad s, NH_2), 1.62 (1H, ds, $CHMe_2$), 3.45 (1H, dd, ^3J= 10.5 and 2.40 Hz, $CH\text{-}NH_2$), 3.70 (1H, d, ^3J= 10.5 Hz, $CH\text{-}Ph_2$), 7.00-7.40 (10H, m, Ar-H). δ_C 14.2 and 21.5 (CH3), 28.9 ($CH\text{-}Me_2$), 58.1 and 58.9 ($CH\text{-}NH_2$ and $CH\text{-}Ph_2$), 126.5, 126.7, 128.2, 128.5, 128.8 and 129.0 (o-, m- and p-Ar), 143.5 (2xα-Ar). Anal. Calcld for $C_{17}H_{21}N$: C 85.30; H 8.84; N 5.85. Found: C 85.12; H 8.91; N 5.96. ir 3361 (NH_2). m/e (CI-CH_4) 240 (MH^+, 8 %), 72 (100 %).

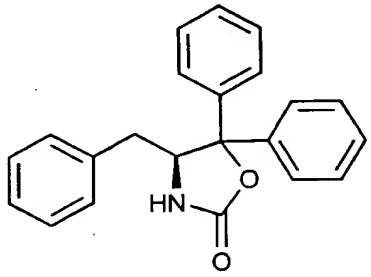
1.2.4 (S)-2-Amino-1,1,3-triphenyl-1-propanol (6)



(6)

L-Phenylalanine ethyl ester hydrochloride (9.9 g, 43.1 mmol) was added portionwise to a 1.0 M solution of phenylmagnesium bromide (63.46 g, 0.35 mol) in THF at 0 °C and stirred for 20h at room temperature. After quenching with crushed ice and concentrated HCl, the aqueous layer was separated and evaporated to dryness under reduced pressure. The resulting solid was washed with diethyl ether and AcOEt to obtain a white gummy HCl-salt. Upon basification with NaOH (1.0 M), organic products were extracted into diethyl ether and AcOEt, dried over $MgSO_4$, and concentrated under reduced pressure to obtain a crude product. Re-crystallisation from a mixture of AcOEt and diethyl ether gave the title compound **(6)** (1.16 g, 9 %) as a white solid. m.p. 141-142 °C (lit[ii] 144-145 °C; lit[vi] 143-144 °C). $[\alpha]_D^{25}$ = - 88.40° (c, 0.0181 in $CHCl_3$) (lit[ii]: - 88.50° (c, 0.604 in $CHCl_3$); lit[vi]: - 94.3° (c, 2.30 in $CHCl_3$). δ_H 2.38 (1H, dd, ^3J= 10.8 Hz, ^2J= 13.8 Hz, CH_2-Ph), 2.58 (1H, dd, ^3J= 2.4 Hz, ^2J= 13.8 Hz, CH_2-Ph), 4.11 (1H, dd, ^3J= 2.4 Hz, ^3J= 10.8 Hz, CH-NH_2), 7.06-7.62 (15H, m, Ar-H). δ_C 36.9 (CH_2-Ph), 58.4 (CH-NH_2), 78.7 (C-OH), 125.6, 126.0, 126.6, 126.7, 126.9, 128.4, 128.7, 128.8 and 129.3 (o-, m- and p-Ar), 139.8, 144.5 and 147.0 (α-Ar). ir 3365 (NH_2), 3320 (OH). m/e (CI-NH_3) 304 (MH^+, 30 %), 271 (100 %).

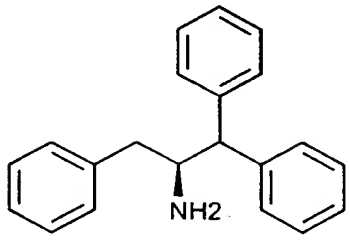
1.2.5 (S)-4-benzyl-5,5-diphenyl -2-oxazolidinone (7)



(7)

Trichloromethyl chloroformate (718 mg, 3.63 mmol) was added to a mixture of (S)-2-amino-1,1,3-triphenyl-1-propanol **(6)** (1.00 g, 3.30 mmol) and triethylamine (710 mg, 7.02 mmol) in CH_2Cl_2 at 0 °C. The reaction mixture was stirred for 5h at the same temperature and then poured into a brine solution (150 ml). The aqueous layer was made basic with powdered K_2CO_3 and organics were extracted into dichloromethane (3x50 ml). The combined organic extracts were dried over $MgSO_4/K_2CO_3$ and concentrated under reduced pressure. The resulting crude product was washed with diethyl ether to obtain the title compound **(7)** (1.06 g, 97 %) as a white solid. m.p. 259-261 °C (lit ? °C). $[\alpha]_D^{25}$ = -241.94° (c, 0.0211 in DMSO), δ_H (DMSO-d_6) 2.18 (1H, dd, ^3J= 10.8 Hz, ^2J= 13.8 Hz, CH_2-Ph), 2.52 (1H, dd, ^3J= 3.6 Hz, ^2J= 13.8 Hz, CH_2-Ph), 4.67 (1H, dd, ^3J= 3.6 Hz, ^3J= 10.8 Hz, CH-NH_2), 6.90-7.60 (15H, m, Ar-H). δ_C 44.2 (CH_2-Ph), 50.5 (CH-NH), 94.1 (C-O), 130.5, 130.9, 131.5, 132.6, 132.8, 133.0, 133.1, 133.3 and 133.4 (o-, m- and p-Ar), 141.1, 143.4 and 146.5 (α-Ar), 163.7 (C=O). ir 3248 (NH_2), 1760 and 1725 (C=O). m/e (CI-NH_3) 330 (MH^+, 5 %), 347 (MNH_4^+, 6 %), 196 (100 %).

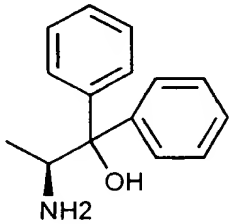
1.2.6 (S)-2-Amino-1,1,3-triphenyl-propane (8)



(8)

A solution of (S)-4-benzyl-5,5-diphenyl-2-oxazolidinone **(7)** (940 mg, 2.85 mmol) in MeOH/AcOH and a 10 % Pd (121 mg, 1.14 mmol) on activated carbon was shaken for 43h under 4-5 atm pressure of hydrogen at room temperature. The catalyst was filtered off over Hyflo Super Cell and organic solvents were evaporated under reduced pressure. The resulting residue was treated with HCl, stirred for 2h at room temperature, made basic with NaOH pellets, and saturated with K_2CO_3 and NaCl. Organics were then extracted into dichloromethane (4x 50 ml), dried over $MgSO_4/K_2CO_3$ and concentrated under reduced pressure to obtain a crude product. Purification over silica gel, eluting with a 3:7 and 4:6 mixture of AcOEt and petroleum ether, gave the title compound **(8)** (584 mg, 71 %) as a light-brown solid. m.p. 71-72 °C. $[\alpha]_D^{25} = -8.03°$ (c, 0.1046 in $CHCl_3$). δ_H 1.21 (2H, broad s, NH_2), 2.29 (1H, dd, ^3J= 9.6 Hz, ^2J= 13.5 Hz, CH_2-Ph), 2.79 (1H, dd, ^3J= 2.1 Hz, ^2J= 13.2 Hz, CH_2-Ph), 3.71 (1H, d, ^3J= 9.9 Hz, CH-Ph_2), 3.81 (1H, ddd, ^3J= 2.7, 9.9 and 12.6 Hz, CH-NH_2), 7.06-7.33 (15H, m, Ar-H). δ_C 41.9 (CH_2-Ph), 55.7 and 59.7 (CH-Ph_2 and CH-NH_2), 126.3, 126.5, 126.6, 128.1, 128.2, 128.4, 128.7, 128.8 and 129.1 (o-, m- and p-Ar), 139.7, 142.6 and 143.1 (α-Ar). ir 3387 (NH_2). m/e (CI-NH_3) 288 (MH^+, 100 %).

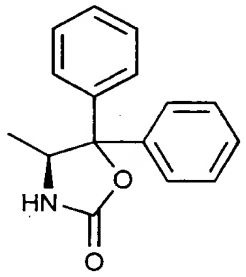
1.2.7 (S)-2-Amino-1,1-diphenyl-1-propanol (10)



(10)

L-Alanine methyl ester hydrochloride (9.9 g, 70.9 mmol) was added portionwise to a 1.0 M solution of phenylmagnesium bromide (78.0 g, 0.43mol) in THF at 0 °C and then heated under reflux for 21h. The reaction mixture was cooled to 0 °C, quenched with dropwise addition of saturated NH_4Cl, and stirred for 1h. After collecting insoluble products through the Buchner funnel, organic products were extracted into AcOEt (3x100 ml). The combined organic extracts were dried over $K_2CO_3/MgSO_4$, and concentrated under reduced pressure to obtain a crude product. Impurities were washed with dichloromethane over silica gel by means of dry-flash column chromatography, further elution with a mixture of AcOEt and petrol, ranging from 20 % up to100 %, gave the title compound **(10)** (1.16 g, 9 %) as a white solid. m.p. 100-101 °C (lit[ii,v] 100-102 °C). $[\alpha]_D^{25} = -85.59°$ (c, 0.0362 in $CHCl_3$) (lit[ii]: -82.38° (c, 0.814 in $CHCl_3$; lit[v]: -85.9° (c, 2.77 in $CHCl_3$). δ_H 0.94 (3H, d, ^3J= 6.30 Hz, CH_3), 1.23 (2H, broad s, NH_2), 4.15 (1H, q, ^3J= 6.30 Hz, CH-NH_2), 4.25 (1H, broad s, OH), 7.10-7.66 (10H, m, Ar-H). δ_C 17.4 (CH_3), 52.1 (CH-NH_2), 78.7 (C-OH), 125.7, 126.1, 126.6, 126.9, 128.2 and 128.7 (o-, m- and p-Ar), 145.0 and 147.2 (α-Ar). Anal. Calcld. for $C_{15}H_{17}NO$: C 79.26; H 7.54; N 6.16. Found: C 79.30; H 7.66; N 6.27. ir 3432 (OH), 3389 (NH_2). m/e (CI-NH_3) 228 (MH^+, 100 %).

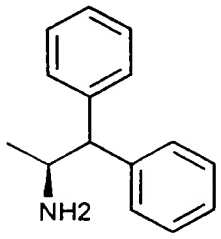
1.2.8 (S)-4-Methyl-5,5-diphenyl-2-oxazolidinone (11)



(11)

Trichloromethyl chloroformate (6.37 g, 32.19 mmol) was added to a mixture of (S)-2-amino-1,1-diphenyl-1-propanol **(10)** (6.65 g, 29.26 mmol) and triethylamine (6.31 g, 62.3 mmol) in CH_2Cl_2 at 0 °C. The reaction mixture was stirred for 5h at the same temperature, poured into a brine solution (150 ml), and diluted with more dichloromethane. After collecting insoluble impurities through the Buchner funnel, the organic layer was separated and the aqueous layer was washed once with a mixture of dichloromethane and AcOEt. The combined organic extracts were dried over $MgSO_4/K_2CO_3$ and concentrated under reduced pressure. The resulting crude product was washed with diethyl ether, water, AcOEt and diethyl ether again, to obtain the title compound **(11)** (5.67 g, 76 %) as a white solid. m.p. 264-266 °C $[\alpha]_D^{25}$ = -279.71° (c, 0.0414 in DMSO). δ_H 0.82 (3H, d, ^3J= 6.30 Hz, CH_3), 4.65 (1H, q, ^3J= 6.0 Hz, CH-NH_2), 7.10-7.70 (10H, m, Ar-H), 7.93 (1H, broad s, NH). δ_C 19.6 (CH_3), 55.9 (CH-NH_2), 85.6 (C-O), 126.3, 126.4, 128.1, 128.6, 128.8 and 129.1 (o-, m- and p-Ar), 140.6 and 144.2 (α-Ar), 157.6 (C=O). ir 3254(NH), 1745 and 1725 (C=O). m/e (CI-NH_3) 254 (MH^+, 9 %), 271 (MNH_4^+, 55 %), 52 (100 %).

1.2.9 (S)-2-Amino-1,1-diphenyl-propane (12)



(12)

A suspension of (S)-4-methyl-5,5-diphenyl-2-oxazolidinone **(11)** (3.52 g, 13.90 mmol) in MeOH/AcOH and a 10 % Pd (148 mg, 1.39 mmol) on activated carbon was shaken for 45h under 4-5 atm pressure of hydrogen at room temperature. The catalyst was filtered off over Hyflo Super Cell and organic solvents were evaporated under reduced pressure. The resulting residue was treated with HCl (2M, 100 ml), stirred overnight at room temperature, made basic with NaOH pellets, and saturated with K_2CO_3. The organics were then extracted into diethyl ether (3x 100 ml), dried over $MgSO_4/K_2CO_3$ and concentrated under reduced pressure to obtain a crude product. Impurities were washed with AcOEt over silica gel by means of dry-flash column chromatography, and then further elution with a mixture of MeOH and AcOEt, ranging from 5 % up to 30 %, gave the title compound **(12)** (1.90 g, 65 %) as a white solid. m.p. 76-77 °C. $[\alpha]_D^{25}$ = - 19.32 (c, 0.10765 in $CHCl_3$). δ_H 1.04 (3H, d, ^3J= 6.30 Hz, CH_3), 1.31 (2H, broad s, NH_2), 3.55 (1H, d, J= 9.90 Hz, CH-Ph_2), 3.73 (1H, dq, ^3J= 6.30 and 10.20 Hz, CH-NH_2), 7.10-7.40 (10H, m, Ar-H). δ_C 22.4 (CH_3), 50.3 (CH-NH_2), 62.4 (CH-Ph_2), 126.5, 126.8, 128.2, 128.5, 128.7 and 129.0 (o-, m- and p-Ar), 143.3 and 143.7 (α-Ar). Anal. Calcld for $C_{15}H_{17}NO$: C 85.26; H 8.11; N 6.63. Found: C 85.10; H 8.08; N 6.36. ir 3343 (NH_2). m/e (CI-NH_3) 212 (MH^+, 100 %).